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(57) Abstract

The present invention relates to a medicine which comprises a combination of a protein possessing cell growth factor activity with a proton pump inhibitor which enhances the preventive and therapeutic effect of either drug used alone against ulcers, particularly peptic ulcers.

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DESCRIPTION

AN ANTIULCER MEDICINE COMPRISING A PROTEIN POSSESSING CELL GROWTH FACTOR ACTIVITY AND A PROTON PUMP INHIBITOR

Technical Field

The present invention relates to a medicine which comprises a combination of a protein possessing cell growth factor activity with a proton pump inhibitor. More specifically, the present invention relates to an antiulcer medicine effective in the prevention and treatment of ulcers, particularly peptic ulcers in mammals.

Background Art

Ulcers occur by various causes. Peptic ulcers are thought to occur due to deterioration of the balance between aggressive factors (factors that adversely affect the gastrointestinal mucosal membrane), such as gastric juice, pepsin, bile and food, and protective factors, such as mucosal membrane blood flow, mucus secretion and carbonate ion secretion. Based on this idea, there is need for peptic ulcer therapy involving the suppression of aggressive factors or enhancement of protective factors; many drugs exhibiting such actions have been developed and are now in wide use.

Well-known aggressive factor suppressors are acid secretion suppressors, such as histamine H_2 receptor blockers (e.g., cimetidine, ranitidine, famotidine, loxatidine), muscarine receptor blockers (e.g. pirenzepine) and proton pump inhibitors (e.g. omeprazole, lansoprazole). On the other hand, well-known protective factor enhancers include prostaglandin derivatives (e.g., misoprostol, ornoprostil) and sucralfate.

Thanks to the development of these drugs, the prevention and treatment of upper gastrointestinal tract ulcerative and inflammatory lesions, such as reflux

esophagitis, gastritis, gastric ulcer, duodenal ulcer and anastomotic ulcer, have recently improved significantly.

However, intractable ulcers remain refractory to treat using these drugs. Ulcerative lesions caused by oral intake of non-steroidal anti-inflammatory agents, such as indomethacin and aspirin, pose another major problem as intractable diseases. In addition, it is known that ulcers, even once healed with the above-described drugs, often recur after medication is discontinued. There is need for new drugs or advanced therapies offering solutions to these problems. The suppressors and enhancers are thought to indirectly promote ulcer healing by providing favorable healing conditions, rather than by directly promoting mucosal cell growth. In recent years, various growth factors have been found to play a key role in the healing of wounds, including those in the gastrointestinal mucosa; for example, acidic and basic fibroblast growth factors and muteins thereof promote the healing of digestive ulcers (Folkman J. et al.: Annals of Surgery 214, 414-427(1991), Fitzpatrick L.R. et al.: Digestion 53, 17-27(1992), Konturek S.J. et al.: Gut 34, 881-887(1993), Szabo S. et al.: Gastroenterology 106, 1106-1111(1994), Satoh H. et al.: Gastroenterology 100, A155(1991) and Gastroenterology 102, A159(1992)). As concerns the mechanism of action of these factors, it has been suggested that they exhibit almost no inhibition of aggressive factors and no enhancement of protective factors, but positively promote ulcer healing by, for example, promoting angiogenesis in the ulcer base, resulting in decreased ulcer recurrence rates (Gastroenterology 102, A159(1992)).

Disclosure of Invention

Through investigations using a rat model of aspirin-induced gastric ulcer, the present inventors found that when a proton pump inhibitor and a fibroblast growth factor are used in combination, the antiulcer effect is definitely

better than with either drug alone. The inventors made further investigations based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

(1) A medicine which comprises a combination of a protein possessing cell growth factor activity with a proton pump inhibitor,

(2) A medicine of term (1) above, wherein the protein possessing cell growth factor activity is a protein possessing fibroblast growth factor activity,

(3) A medicine of term (2) above, wherein the protein possessing fibroblast growth factor activity is a protein possessing basic fibroblast growth factor activity,

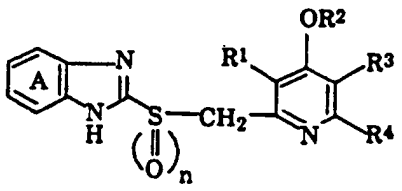
(4) A medicine of term (3) above, wherein the protein possessing basic fibroblast growth factor activity is acid-resistant,

(5) A medicine of term (3) above, wherein the protein possessing basic fibroblast growth factor activity is a basic fibroblast growth factor (bFGF) mutein showing enhanced acid stability as a result of replacement of at least one bFGF-constituent cysteine with another amino acid,

(6) A medicine of term (5) above, the bFGF mutein is the recombinant human bFGF mutein CS23 in which cysteine residues at the 70- and 88- positions are replaced by serine residues,

(7) A medicine of term (1) above, wherein the proton pump inhibitor is a benzimidazole compound,

(8) A medicine of term (7) above, wherein the benzimidazole compound is a compound of the formula:



wherein ring A may optionally be substituted, R^1, R^3 and R^4 are, the same or different, hydrogen, or an alkyl or alkoxy group, R^2 is a hydrocarbon group which may optionally be substituted, and n is 0 or 1, or a salt thereof,

(9) A medicine of term (8) above, wherein the compound is lansoprazole,

(10) A medicine of term (1) above, which comprises a combination of the mutein CS23 with lansoprazole,

(11) A medicine of term (1) above, which is used to prevent or treat an ulcer,

(12) A medicine of term (11) above, wherein the ulcer is a peptic ulcer,

(13) A medicine of term (1), which is a kit which comprises a protein possessing cell growth factor activity and a proton pump inhibitor,

(14) A medicine of term (1), which is a pharmaceutical composition which comprises a protein possessing cell growth factor activity and a proton pump inhibitor,

(15) A method of producing a pharmaceutical composition which comprises admixing a protein possessing cell growth factor activity with a proton pump inhibitor,

(16) Use of a combination of a protein possessing cell growth factor activity with a proton pump inhibitor for the manufacture of a medicine for the prevention or treatment of an ulcerative disease,

(17) A method for preventing or treating a ulcerative disease of a mammal, which comprises administering an effective amount of a protein possessing cell growth factor activity in combination with an effective amount of a proton pump inhibitor to the mammal, and

(18) A method of use of a proton pump inhibitor for enhancing a protein possessing cell growth factor activity.

A cell growth factor is defined as a non-nutrient substance that promotes animal cell growth *in vivo* or *in vitro*; the term "protein possessing cell growth factor

activity" as used herein includes all proteins possessing such activity, as long as they are of low toxicity. Examples of such cell growth factors include fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epithelial cell growth factor (EGF), α- and β-transforming growth factors (TGFα, TGFβ), insulin-like growth factor (IGF) and platelet-derived angiogenesis factor (PD-ECGF). These proteins possessing cell growth factor activity may be isolated from animal bodies and purified, or produced by gene engineering, and as long as they retain their cell growth factor activity, may be muteins resulting from appropriate modifications of constituent amino acids of natural proteins, such as deletion and replacement of some constituent amino acids, and addition of other amino acids.

Proteins possessing fibroblast growth factor (FGF) activity include proteins possessing acidic fibroblast growth factor (aFGF) activity and proteins possessing basic fibroblast growth factor (bFGF) activity, with preference given to proteins possessing bFGF activity.

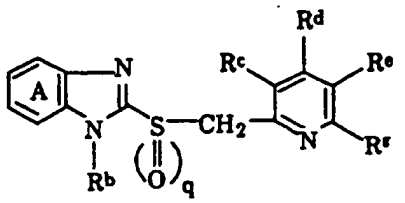
Proteins possessing bFGF activity is preferably acid-resistant.

Proteins possessing fibroblast growth factor (FGF) activity include acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), and muteins thereof. Example bFGF muteins include those described in Japanese Patent Unexamined Publication No. 193/1990 and Japanese Publication of translations of International patent application No. 505736/1991. Preferable muteins are (1) muteins resulting from replacement of at least one bFGF-constituting amino acid with another amino acid, (2) the muteins of term (1) above, wherein said bFGF-constituting amino acid is cysteine, (3) the muteins of term (1) above, wherein said other amino acid is a neutral amino acid, and (4) the muteins of term (1) above, wherein at least one cysteine, as a constituent amino acid, is replaced with serine. For exampale, the muteins include a modified bFGF

such as a purified recombinant human basic FGF (rhbFGF) protein in which a mutation is induced by changing one or more of the four cysteines present at amino acid residues 25, 69, 87 and 92 of the mature protein to serine. In numbering the human bFGF-constitueny amino acids, the N-terminal Pro comprises the first amino acid. Of these muteins, those showing enhanced acid stability, in comparison with the natural basic fibroblast growth factor, as a result of replacement of at least one bFGF-constituting cysteine with another amino acid, are preferred, with greater preference given to the mutein (CS23) resulting from serine replacement of the cysteine residues (70- and 88-positions) at the second and third positions from the N-terminal side, among the four cysteine residues in the amino acid sequence of human bFGF. The structure of the mutein CS23 is more fully described in Senoo et al., Biochemical and Biophysical Communications, Vol.151, No.2, 702-708 (1988) and in EP-281,822.

The term proton pump inhibitor as used herein is defined as a drug that suppresses acid secretion by directly or indirectly inhibiting H/K-ATPase, which functions as a proton pump in gastric mucosal acid secreting cells (parietal cells). Examples of such drugs include omeprazole, lansoprazole, pantoprazole, pariprazole sodium, leminoprazole, TY-11345, TU-199, FPL-65372, BY-686, Tannic acid, Ellagic acid, Ebselen, AHR-9294, Cassigarol-A, Bafilomycin, Y-25942, Xanthoangelol E, SK&F-96356, (-)-Epigallocatechin gallate, WY-27198, T-330 and KF-20054.

Especially, proton pump inhibitors include benzimidazole compounds, which possess proton pump inhibitory activities and are of low toxicity. Preferable benzimidazole compounds include 2-[(pyridyl)-methylsulfinyl or -methylthio]benzimidazole derivatives and salts thereof. A compound (or salt thereof) represented by formula (I) below is more preferred.



(I)

wherein ring A may optionally be substituted; R^b is a hydrogen atom, an alkyl group, an acyl group, a carboalkoxy group, a carbamoyl group, an alkylcarbamoyl group, a dialkylcarbamoyl group or an alkylsulfonyl group; R^c, R^e, and R^g are, the same of different, a hydrogen atom, an alkyl group, an alkoxy group or an alkoxyalkoxy group; R^d is a hydrogen atom, an alkyl group or a group represented by $-OR^f$ in which R^f represents a hydrocarbon group which may optionally be substituted; q is 0 or 1.

Benzimidazole compounds above are described in USP 4,045,563, USP 4,255,431, USP 4,359,465, USP 4,472,409, USP 4,508,905, JP-A-59181277, USP 4,628,098, USP 4,738,975, USP 5,045,321, USP 4,786,505, USP 4,853,230, USP 5,045,552, EP-A-295603, USP 5,312,824, EP-A-166287, EP-A- 519365, and other publications.

With respect to formula (I) above, the substituent that may optionally be present on ring A includes halogen atoms, alkyl groups which may be substituted for, cycloalkyl groups which may be substituted for, alkenyl groups which may be substituted for, alkoxy groups which may be substituted for, cyano groups, carboxy groups, carboalkoxy groups, carboalkoxyalkyl groups, carbamoyl groups, carbamoylalkyl groups, hydroxy groups, hydroxyalkyl groups, acyl groups, carbamoyloxy groups, nitro groups, acyloxy groups, aryl groups, aryloxy groups, alkylthio groups and alkylsulfinyl groups, and the like.

The above substituents are hereinafter described.

Halogen atoms include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are preferred, with greater preference given to fluorine.

The alkyl group in the alkyl group which may be substituted is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms. Substituents on the substituted alkyl group include halogens, nitro, cyano groups, hydroxy groups, carboxy groups, amidino groups, guanidino groups , carbamoyl groups, amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like.

The cycloalkyl group in the cycloalkyl group which may be substituted is exemplified by cycloalkyl groups having 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl etc.. The cycloalkyl group may be substituted by, for example, halogens, nitro, cyano groups, hydroxy groups, carboxy groups, amidino groups, guanidino groups , carbamoyl groups, amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like.

The alkenyl group in the alkenyl group which may be substituted is exemplified by straight-chain or branched alkenyl groups having 2 to 16 carbon atoms. Such alkenyl groups include allyl, vinyl, crotyl, 2-penten-1-yl, 3-penten-1-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-methyl-2-propen-1-yl and 3-methyl-2-buten-1-yl. Straight-chain or branched alkenyl groups having 2 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkenyl groups having 2 to 4 carbon atoms. The alkenyl group may be substituted by, for example, halogens, nitro, cyano groups, amidino groups , guanidino groups amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like . The alkenyl group

mentioned above includes isomers (E- and Z-configurations) with respect to double bond.

The alkoxy group in the alkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 10 carbon atoms. Such alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy. Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms. The alkoxy group may be substituted by, for example, halogens, nitro, amidino groups , guanidino groups amino groups which may have 1 to 2 alkyl groups, acyl groups or other substituents, and the like .

The halogen as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is exemplified by chlorine, bromine, fluorine and iodine.

The alkyl group in the alkylamino group as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is preferably exemplified by straight-chain or branched alkyl groups having 1 to 6 carbon atoms. Such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl and isohexyl. Among others, straight-chain or branched alkyl groups having 1 to 4 carbon atoms are preferred.

The acyl group in the acylamino group as a substituent on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is exemplified by acyl groups derived from organic carboxylic acids, with preference given to alkanoyl groups having 1 to 6 carbon atoms. Such alkanoyl groups include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl, with greater preference given to alkanoyl groups having 1 to 4 carbon atoms.

The number of substituents on the above-described alkyl, cycloalkyl, alkenyl or alkoxy group is 1 to 6, preferably 1 to 3.

The substituted alkyl groups include trifluoromethyl, trifluoroethyl, difluoromethyl, trichloromethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, methoxyethyl, ethoxyethyl, 1-methoxyethyl, 2-methoxyethyl, 2,2-dimethoxyethyl, 2,2-diethoxyethyl and 2-diethylphosphorylethyl, among others. Difluoromethyl, trifluoromethyl and hydroxymethyl are preferred, with greater preference given to trifluoromethyl.

The substituted cycloalkyl groups include 2-aminocyclopropan-1-yl, 4-hydroxycyclopentan-1-yl and 2,2-difluorocyclopentan-1-yl, among others.

The substituted alkenyl groups include 2,2-diclorovinyl, 3-hydroxy-2-propen-1-yl and 2-methoxyvinyl, among others.

The substituted alkoxy groups include difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 2-methoxyethoxy, 4-chlorobenzyloxy and 2-(3,4-dimethoxyphenyl)ethoxy, among others. Difluoromethoxy is preferred.

The alkoxy group in the carboalkoxy group is exemplified by alkoxy groups having 1 to 7 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy).

The alkoxy group in the carboalkoxyalkyl group is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy). The alkyl group in the carboalkoxyalkyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl). Such carboalkoxyalkyl groups include carbomethoxymethyl, 2-carbomethoxyethyl, 2-carbomethoxypropyl, carboethoxymethyl,

2-carboethoxyethyl, 1-carbomethoxypropyl, carbopropoxymethyl and carbobutoxymethyl.

The alkyl group in the carbamoylalkyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl).

The alkyl group in the hydroxyalkyl group is exemplified by alkyl groups having 1 to 7 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl).

The acyl group as such or the acyl group in the acyloxy group is exemplified by alkanoyl groups having 1 to 4 carbon atoms such as formyl, acetyl, propionyl, butyryl and isobutyryl.

The aryl group as such or the aryl group in the aryloxy group is exemplified by aryl groups having 6 to 12 carbon atoms (e.g., phenyl, naphthyl).

The alkyl in the alkylthio group or alkylsulfinyl group is exemplified by alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl).

The number of substituents on substituted ring A is preferably 1 to 4, more preferably 1 to 2. Such substituents on the benzene ring may be present at 4- and 5-positions, with preference given to 5-position.

Ring A is preferably A ring which may optionally be substituted by i) a halogen atom ii), an alkyl group which may be substituted, iii) a cycloalkyl group which may be substituted, iv) an alkenyl group which may be substituted, or v) an alkoxy group which may be substituted.

The alkyl group for R^b is exemplified by alkyl groups having 1 to 5 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl). The acyl group for R^b is

exemplified by acyl groups having 1 to 4 carbon atoms, such as alkanoyl groups having 1 to 4 carbon atoms. The alkoxy in the carboalkoxy group is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl). The alkyl in the alkylcarbamoyl group and dialkylcarbamoyl group is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl). The alkyl in the alkylsulfonyl group is exemplified by the above-mentioned alkyl groups having 1 to 4 carbon atoms. R^b is preferably hydrogen.

The alkyl group for R^c, R^e or R^g is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms.

The alkoxy group for R^c, R^e or R^g is exemplified by alkoxy groups having 1 to 10 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy). Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms.

The alkoxy in the alkoxyalkoxy group for R^c, R^e or R^g is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy).

R^c is preferably a hydrogen atom, an alkyl group or an alkoxy group. R^e is preferably a hydrogen atom, an alkyl

group or an alkoxy group. R^g is preferably a hydrogen atom.

The alkyl group for R^d is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl).

The hydrocarbon group in the hydrocarbon group which may optinally be substituted, for R^f, is exemplified by hydrocarbon groups having 1 to 13 carbon atoms, such as straight-chain or branched alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl, hexyl), alkenyl groups having 2 to 6 carbon atoms (e.g., vinyl, allyl, 2-butenyl, methylallyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 5-hexenyl), alkinyl groups having 2 to 6 carbon atoms (e.g., ethynyl, propargyl, 2-butyn-1-yl, 3-butyn-2-yl, 1-pentyn-3-yl, 3-pentyn-1-yl, 4-pentyn-2-yl, 3-hexyn-1-yl), cycloalkyl groups having 3 to 6 carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), cycloalkenyl groups having 3 to 6 carbon atoms (e.g., cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl), aralkyl groups having 7 to 13 carbon atoms (e.g., benzyl, 1-phenetyl, 2-phenetyl) and aryl groups having 6 to 10 carbon atoms (e.g., phenyl, naphthyl). Straight-chain or branched alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, isopentyl, hexyl) are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 4 carbon atoms.

The substituent group in the substituted hydrocarbon group is exemplified by C_{6-10} aryl groups (e.g., phenyl, naphthyl), amino, C_{1-6} alkylamino groups (e.g., methylamino, ethylamino, isopropylamino), di-C_{1-6} alkylamino groups (e.g., dimethylamino, diethylamino), N-aralkyl-N-cycloalkylamino groups (e.g., N-benzyl-N-cyclohexylamino), N-aralkyl-N-alkylamino groups (e.g., N-

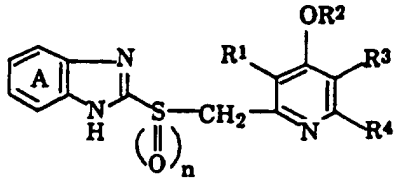
(1-naphthylmethyl)-N-ethylamino), azide, nitro, halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl, C_{1-4} alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy), C_{6-10} aryloxy groups (e.g., phenoxy, naphthyloxy), C_{1-6} alkylthio groups (e.g., methylthio, ethylthio, propylthio), C_{6-10} arylthio groups (e.g., phenylthio, naphthylthio), cyano, carbamoyl groups, carboxyl groups, C_{1-4} alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl), C_{7-11} aryloxycarbonyl groups (e.g., phenoxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl), carboxy-C_{1-4} alkoxy groups (e.g., carboxymethoxy, 2-carboxyethoxy), C_{1-6} alkanoyl groups (e.g., formyl, acetyl, propionyl, isopropionyl, butyryl, pentanoyl, hexanoyl), C_{7-11} alloyl groups (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C_{6-10} arylsulfonyl groups (e.g., benzenesulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl), C_{1-6} alkylsulfinyl groups (e.g., methylsulfinyl, ethylsulfinyl), C_{6-10} arylsulfinyl groups (e.g., benzenesulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl), C_{1-6} alkylsulfonyl groups (e.g., methylsulfonyl, ethylsulfonyl), 5- or 6-membered heterocyclic groups (e.g., 2-furyl, 2-thienyl, 4-thiazolyl, 4-imidazolyl, 4-pyridyl, 1,3,4-thiadiazol-2-yl, 1-methyl-5-tetrazolyl) containing 1 to 4 hetero atoms (e.g., nitrogen, oxygen, sulfur), 5- or 6-membered heterocyclic carbonyl groups (e.g., 2-furoyl, 2-thienoyl, nicotinoyl, isonicotinoyl) containing 1 to 4 hetero atoms (e.g., nitrogen, oxygen, sulfur), 5- or 6-membered heterocyclic thio groups (e.g., 4-pyridylthio, 2-pyrimidylthio, 1,3,4-thiadiazol-2-ylthio, 1-methyl-5-tetrazolylthio) containing 1 to 4 hetero atoms (e.g., nitrogen, oxygen, sulfur). The heterocyclic thio group may condense with the benzene ring to form a bicyclic condensed thio group (e.g., 2-benzothiazolylthio, 8-quinolylthio). Halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl and C_{1-4} alkoxy groups (e.g., methoxy, ethoxy, propoxy, butoxy) are preferred.

The number of substituents is normally 1 to 5, preferably 1 to 3.

R^d is preferably an alkoxy group which may be substituted, or an alkoxyalkoxy group which may be substituted. The alkoxy in the alkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 8 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy). The alkoxy in the alkoxyalkoxy group which may be substituted is exemplified by alkoxy groups having 1 to 4 carbon atoms (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy). R^d is more preferably an alkoxy group having 1 to 8, preferably 1 to 4 carbon atoms, which may be halogenated, or an alkoxyalkoxy group which may be halogenated. Preferred alkoxy groups which may be halogenated include 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy, 2,2,3,3,4,4,5,5-octafluoropentoxy and methoxy. Preferred alkoxyalkoxy groups which may be halogenated include 3-methoxypropoxy.

q is preferably 0.

More specifically, the benzimidazole compound for the present invention is exemplified by a compound represented by formula (II):



(II)

wherein ring A may optionally be substituted; R^1, R^3 and R^4 are, the same or different, hydrogen, or an alkyl or alkoxy group; R^2 is a hydrocarbon group which may optionally be substituted; n is 0 or 1.

With respect to formula (II) above, ring A is exemplified by the same rings as those mentioned for ring A of formula (I) above.

The alkyl group for R^1, R^3 or R^4 is exemplified by straight-chain or branched alkyl groups having 1 to 10 carbon atoms. Such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl and decyl. Straight-chain or branched alkyl groups having 1 to 6 carbon atoms are preferred, with greater preference given to straight-chain or branched alkyl groups having 1 to 3 carbon atoms.

The alkoxy group for R^1, R^3 or R^4 is exemplified by alkoxy groups having 1 to 10 carbon atoms. Such alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy. Alkoxy groups having 1 to 6 carbon atoms are preferred, with greater preference given to alkoxy groups having 1 to 3 carbon atoms.

The hydrocarbon group which may optionally be substituted, for R^2, is exemplified by the same hydrocarbon groups as those mentioned for R^f above.

R^1 is preferably C_{1-6} alkyl or C_{1-6} alkoxy, more preferably C_{1-3} alkyl.

R^3 is preferably hydrogen or C_{1-6} alky, more preferably hydrogen.

R^2 is preferably C_{1-4} alkoxy which may optionally be substituted by i) halogen, ii) hydroxyl or iii) C_{1-4} alkoxy, more preferably, C_{1-3} alkyl which may optionally be substituted by i) halogen or ii) C_{1-4} alkoxy.

R^4 is preferably hydrogen.

Example benzimidazole compounds for the present invention include 2-[2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridyl]methylthio] benzimidazole, 2-[2-

[3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl]methylsulfinyl]benzimidazole (lansoprazole), 2-[(2-pyridyl)methylsulfinyl]benzimidazole (timoprazole), 2-[2-(3,5-dimethyl-4-methoxypyridyl)methylsulfinyl]-5-methoxy-1H-benzimidazole (omeprazole), sodium salt of 2-[2-[4-(3-methoxypropoxy)-3-methylpyridyl]methylsulfinyl]-1H-benzimidazole and 2-[2-(3,4-dimethoxy)pyridyl]methylsulfinyl]-5-difluoromethoxy-1H-benzimidazole (pantoprazole).

A benzimidazole compound (or salt thereof) for the present invention is produced by, for example, the above-described known methods described in Japanese or European Patent Publications and U.S. Patents, or modifications thereof.

The salt of a benzimidazole compound is preferably used as a physiologically acceptable salt. Physiologically acceptable salts include salts with inorganic bases, salts with organic bases and salts with basic amino acids. Useful inorganic bases include alkali metals (e.g., sodium, potassium) and alkaline earth metals (e.g., calcium, magnesium). Useful organic bases include trimethylamine, triethylamine, pyridine, picoline, N,N-dibenzylethylenediamine, ethanolamine, diethanolamine, trishydroxymethylaminomethane and dicyclohexylamine. Useful basic amino acids include arginine and lysine.

These salts are produced by known methods such as those described in EP-A-295603 and USP 4,738,974, or modifications thereof.

The medicine of the present invention is applicable to the prevention and treatment of animal ulcers, and is particularly effective in the prevention and treatment of digestive ulcers in mammals, including humans. Examples of such digestive ulcers include gastric ulcer, duodenal ulcer, reflux esophagitis, anastomotic ulcer, acute and chronic gastritis.

The medicine of the present invention, characterized by combined use of a protein possessing cell growth factor activity and a proton pump inhibitor, is not subject to limitation as to dosage form. For example, a protein possessing cell growth factor activity and a proton pump inhibitor may be prepared as individual preparations of ordinary dosage form, or as a composition incorporating both.

For an example of the medicine of the present invention, a protein possessing cell growth factor activity (the active ingredient A) and a proton pump inhibitor (the active ingredient B) may be mixed to a single preparation, as desired, using pharmaceutically acceptable diluents, excipients and other additives by a known method of pharmaceutical production. Each active ingredient may be prepared as a separate preparation, as desired, using pharmaceutically acceptable diluents, excipients and other additives. Alternatively, the medicine of the present invention may be prepared in a set (kit) in which each component constitutes a separate preparation. For example, the medicine of the present invention can be used in a form of (1) a kit comprising a protein possessing cell growth factor activity and a proton pump inhibitor or (2) in a form of a composition containing a protein possessing cell growth factor activity and a proton pump inhibitor.

As concerns the route of administration of the antiulcer medicine of the present invention, oral administration is preferable, but non-oral administrations (e.g., intravenous administration, subcutaneous administration, intramuscular administration) are also possible. Proton pump inhibitors, in particular, permit both oral and non-oral administrations. Specifically, the route of administration is determined in consideration of target ulcer site etc.

When a protein possessing cell growth factor activity and a proton pump inhibitor are used as separate preparations, they may be administered to the same individual at the same time or at time intervals via the same route or different routes.

In administering the antiulcer medicine of the present invention, the protein possessing cell growth factor activity and the proton pump inhibitor can be administered in individual dosage forms prepared by conventional methods. For proteins possessing cell growth factor activity, preparations in such dosage forms can, for example, be manufactured by the method described in Japanese Publication of translations of International patent application No. 505736/1991. Specifically, tablets and capsules are prepared using pharmacologically acceptable carriers (e.g., lactose, corn starch, light silicic anhydride, microcrystalline cellulose, sucrose), binders (e.g., alpha-starch, methyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone), disintegrating agents (e.g., carboxymethyl cellulose, starch, low-substitutional hydroxypropyl cellulose), surfactants [e.g., Tween 80 (Kao-Atlas), Prullonic F68 (Asahi Denka, Japan), polyoxyethylene-polyoxypropylene copolymer], antioxidants (e.g., L-cysteine, sodium sulfite, sodium ascorbate), lubricants (e.g., magnesium stearate, talc) and similar substances. An aqueous solution for injection is prepared by a conventional method using an aqueous solvent (e.g., distilled water, physiological saline, Ringer's solution) or an oily solvent (e.g., sesame oil, olive oil). One or more than one additive can be used as necessary. Such additives include dissolution aids (e.g., sodium salicylate, sodium acetate), buffers (e.g., sodium citrate, glycerol), isotonizing agents (e.g., glucose, inverted sugar), stabilizers (e.g., human serum albumin, polyethylene glycol), antiseptics (e.g., benzyl

alcohol, phenol) and analgesics (e.g., benzalkonium chloride, procaine hydrochloride). A solid preparation for injection is prepared by a conventional method using, for example, a diluent (e.g., distilled water, physiological saline, glucose), an activator (e.g., carboxymethyl cellulose, sodium alginate), an antiseptic (e.g., benzyl alcohol, phenol) and an analgesic (e.g., benzalkonium chloride, procaine hydrochloride).

In the case of proton pump inhibitors, the same method as above can normally be used. It is preferable, however, that the proton pump inhibitor be administered in the form of nucleated granules coated with a powder comprising the inhibitor and low-substitutional hydroxypropyl cellulose, according to the method described in Japanese Patent Application Unexamined Publication No. 301816/1988, or a solid composition stabilized with a stabilizer comprising a basic inorganic salt of magnesium and/or calcium, according to the method described in Japanese Patent Application Unexamined Publication No. 163018/1991.

Example compositions comprising a protein possessing cell growth factor activity and a proton pump inhibitor for oral administration include tablets, pills, granules, powders, capsules, syrups, emulsions and suspensions. These compositions are produced by known methods, using lactose, starch, sucrose, magnesium stearate and other substances as carriers or excipients.

Compositions for non-oral administration can be prepared as suppositories or external preparations.

Suppositories include rectal suppositories and vaginal suppositories. External preparations include ointments (including creams), vaginal preparations, transnasal preparations and percutaneous preparations.

For a suppository, a composition of the present invention may be prepared as an oily or aqueous solid, semi-solid or liquid suppository by a known method.

The contents of the protein possessing cell growth factor activity and proton pump inhibitor in the medicine of the present invention may be chosen as appropriate depending on the situation; for example, the concentration of the protein is normally about 0.0001 to 10% by weight, preferably about 0.001 to 1% by weight, and more preferably about 0.01 to 0.2% by weight. The concentration of the proton pump inhibitor is normally about 0.1 to 90% by weight, preferably about 1 to 50% by weight, and more preferably about 2 to 20% by weight.

The ratio of the protein possessing cell growth factor activity used to the proton pump inhibitor is normally about 0.0001 to 1 times (by weight), preferably about 0.001 to 0.1 times (by weight), of the proton pump inhibitor content, although it varies depending on combinations.

With respect to the medicine of the present invention, a protein possessing fibroblast growth factor activity and a proton pump inhibitor, separately prepared, may be administered to the same subject at the same time, or they may be administered to the same subject at a time interval. The components may have different administration frequencies. The administration frequency of the proton pump inhibitor is preferably one or two per day, more preferably one per day. The administration frequency of the protein possessing fibroblast growth factor activity is preferably 1 to 4 per day, more preferably 3 or 4 per day.

In administering the antiulcer medicine of the present invention, it is preferable that the protein possessing cell growth factor activity be in a state in which acid secretion is suppressed by proton pump inhibitor administration (normally after about 30 - 60 minutes following oral administration of the proton pump inhibitor). If acid secretion is continuously suppressed by daily administration of a proton pump inhibitor, the protein can be administered concomitantly with the proton pump inhibitor.

Although the dose of the antiulcer medicine of the present invention is chosen as appropriate, according to ulcer type and symptoms, the protein possessing cell growth factor activity is administered at 0.01 - 1,000 μg/kg/day, preferably 0.1 - 300 μg/kg/day more preferably 0.1 - 10 μg/kg/day, and the proton pump inhibitor at 0.01 mg/kg/day - 10 mg/kg/day, preferably 0.1 - 3 mg/kg/day, more preferably 0.1 - 1 mg/kg/day. The dosage volume per administration is determined in consideration of such daily dose, dosage form etc.

The medicine of the present invention may include, besides a protein possessing cell prowth factor activity and a proton pump inhibitor, an active ingredient such as an antiulcer substance (ex. H_2 blockers).

Best Mode for Carrying Out the Invention

Experimental Example 1

Male Jcl:SD rats (weighing about 220 g) at 7 weeks of age were used in the experiment after being fasted for 24 hours. Each rat received oral administration of lansoprazole suspended in vehicle ① containing 1% $NaHCO_3$ and 0.5% methyl cellulose, or vehicle ① alone. Thirty minutes later, aspirin suspended in 0.5% methyl cellulose (vehicle ②) was orally administered at 200 mg/kg. From 1 hour after aspirin administration, ordinary solid food was given for 2 hours. In experiment 1, CS23 (a human basic fibroblast growth factor mutein) dissolved in vehicle ② containing no $NaHCO_3$, or the vehicle alone, was orally administered three hours later to subject animals. In experiment 2, CS23 dissolved in vehicle ① containing 1% $NaHCO_3$, or the vehicle alone, was orally administered three hours later to subject animals. At 24 hours after aspirin administration, animals were sacrificed with gaseous carbon dioxide; the stomach, together with the lower esophagus and duodenum, was excised from each animal. After the esophagus was clipped, 10 ml of 1% formalin was injected

into the stomach via the duodenum, the whole stomach being immersed in 1% formalin. About 15 minutes later, the stomach was incised along the greater curvature, and the contents removed. The length (mm) of each lesion in the gastric body was measured under a dissecting microscope (×10). For each rat, the length of each lesion was summed, and used as lesion index. The results of experiments 1 and 2 are shown in Tables 1 and 2, respectively.

Table 1 Effects of Lansoprazole and CS23 on Gastric Mucosal lesions Induced by Aspirin in Rats (Experiment 1)

Group	Drug (1)	Drug (2)	Number of Animals	Gastric Mucosal lesion Index (mm)	Inhibition (%)
1	Veh-①	Veh-②	6	73.5 ± 4.8	
2	Veh-①	CS23 (0.1)	6	61.5 ± 6.4	16
3	LPZ (1.0)	Veh-②	6	50.2 ± 8.4	32
4	LPZ (3.0)	Veh-②	6	34.5 ± 3.1 [a]	53
5	LPZ (1.0)	CS23 (0.1)	6	36.0 ± 2.2 [a b]	51
6	LPZ (3.0)	CS23 (0.1)	6	13.0 ± 2.1 [a b c]	82

Drug (1) was orally administered 30 minutes before aspirin administration, and drug (2) 6 hours after aspirin administration.

Veh-①: Solution containing 1% $NaHCO_3$ and 0.5% methyl cellulose

Veh-②: Solution containing 0.5% methyl cellulose

LPZ : Lansoprazole

( ) : Dose (mg/kg, p.o.)

a: $p < 0.05$ vs group 1; b: $p < 0.05$ vs group 2; c: $p < 0.05$ vs group 4

Table 2 Effects of Lansoprazole and CS23 on Gastric Mucosal lesions Induced by Aspirin in Rats (Experiment 2)

Group	Drug (1)	Drug (2)	Number of Animals	Gastric Mucosal lesion Index (mm)	Inhibition (%)
1	Veh-①	Veh-①	6	76.3 ± 11.6	-
2	Veh-①	CS23 (0.1)	6	45.5 ± 4.3	40
3	LPZ (1.0)	Veh-①	6	43.8 ± 5.9	43
4	LPZ (3.0)	Veh-①	6	28.2 ± 4.2 [a]	63
5	LPZ (1.0)	CS23 (0.1)	6	29.0 ± 5.5 [a b]	62
6	LPZ (3.0)	CS23 (0.1)	6	15.7 ± 2.2 [a b c]	79

Drug (1) was orally administered 30 minutes before aspirin administration, and drug (2) 6 hours after aspirin administration.

Veh-①: Solution containing 1% $NaHCO_3$ and 0.5% methyl cellulose

LPZ : Lansoprazole

( ) : Dose (mg/kg, p.o.)

a: $p < 0.01$ vs group 1; b: $p < 0.05$ vs group 2; c: $p < 0.05$ vs group 4

As shown in Tables 1 and 2, lansoprazole (1 and 3 mg/kg) dose-dependently decreased the gastric mucosal lesion index in both experiments, the index for the 3 mg/kg group being significantly lower than that for the control group, which received vehicle alone. CS23 (0.1 mg/kg) showed no action in experiment 1, in which it was administered with vehicle ② not containing 1% $NaHCO_3$, but caused a 40% reduction in experiment 2, in which it was administered with vehicle ①, containing 1% $NaHCO_3$. Combined use of lansoprazole and CS23 resulted in marked decrease in lesion index; the lesion indexes for group 6, which received 3 mg/kg lansoprazole and 0.1 mg/kg CS23,

were significantly lower than those for the respective single-drug groups.

These results demonstrate that combined use of the two drugs is useful in the prevention and treatment of ulcers.

Preparation Examples

The medicine of the present invention can be, for example, produced with the following formulations.

1. Capsule

(1) lansoprazole	10 mg
(2) CS23	0.1 mg
(3) Lactose	90 mg
(4) Microcrystalline cellulose	70 mg
(5) Magnesium stearate	10 mg
Total	180.1 mg per capsule

Components (1), (2), (3) and (4) and a half portion of component (5) are mixed and granulated. To these granules, the remaining portion of component (5) is added, and the whole mixture is packed in a gelatin capsule.

2. Tablet

(1) lansoprazole	10 mg
(2) CS23	0.1 mg
(3) Lactose	35 mg
(4) Corn starch	150 mg
(5) Microcrystalline cellulose	30 mg
(6) Magnesium stearate	5 mg
Total	230.1 mg per tablet

Components (1), (2), (3) and (4), a two-third portion of component (5) and a half portion of component (6) are mixed and granulated. To these granules, the remaining portions of components (5) and (6) are added, and the whole mixture is tableted by compressive tableting.

3. Kit

A kit in which each component constitutes a separate preparation is prepared with the capsules A and B.

(a) capsule A

(1) lansoprazole	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Total	180 mg per capsule

Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules, the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

(b) capsule B

(1) CS23	0.1 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Total	170.1 mg per capsule

Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules, the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

4. kit

A kit in which each component constitutes a separate preparation is prepared with the capsules B and C.

(a) capsule B

(1) CS23	0.1 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Total	170.1 mg per capsule

Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules,

the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

(b) capsule C

Nonpareils (Trade-mark), 1650 g, [sugar core prepared by coating sucrose (75 weight parts) with corn starch (25 weight parts) according to a per se known method, 20 to 28 mesh] are brought into the CF (Trade-mark) granulator (CF-360, Freund Industrial Co., Ltd., Japan), and coated, while being sprayed with 1050 mℓ of a hydroxypropylcellulose solution [2% (w/v)] at 30 mℓ/min., first with the spraying powder 1 and then with the spraying powder 2, both of which are prepared by mixing the ingredients listed below, at the rate of 60 g/min. at room temperature with a rotor rotating at 200 rpm, dried in vacuo at 40°C for 16 hours, and sieved through round sieves, to give spherical granules (14 to 32 mesh) having a core.

[spraying powder 1]

lansoprazole	450 g
magnesium carbonate	336 g
granulated sugar	297 g
corn starch	300 g
L-HPC	354 g
[degree of substitution with hydroxypropaxyl group: 10.0 to 13.0% (w/w), mean particle size : not more than 30 μm]	

[spraying powder 2]

granulated sugar	300 g
corn starch	246 g
L-HPC (the same one as above)	246 g

The granules obtained as above, 3,800 g, are brought into a fluidized-bed coating vessel (Ohkawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50

mℓ/min. under the controlled conditions of inlet air at 65°C and material temperature at 40°C, to give enteric coated spherical granules having a core.

The said granules are mixed with talc and light anhydrous silicic acid, then the mixture is filled into No. 1 hard capsules with a capsule filling machine (Parke-Davis & Co., USA) to give capsules.

[Enteric coating film solution]

Endragit L30D-55	2,018 g (solid: 605g)
talc	182 g
polyethyleneglycol 6000	60 g
titanium oxide	60 g
Tween 80	27 g
water	4,230 mℓ

[composition in one capsule]

enteric coated granules	368.8 mg
lansoprazole	30.0 mg
magnesium carbonate	22.4 mg
Nonpareils	110.0 mg
granulated sugar	59.8 mg
corn starch	36.4 mg
L-HPC	40.0 mg
hydroxypropylecllulose	1.4 mg
Eudragit L30D-50	44.6 mg
talc	13.4 mg
polyethyleneglycol 6000	4.4 mg
titanium oxide	4.4 mg
tween 80	2.0 mg
talc	0.6 mg
light anhydrous silicic acid	0.6 mg
No. 1 hard capsule	79.0 mg
Total	449.0 mg

Industrial Applicability

Combined use of a protein, possessing cell growth factor activity, and a proton pump inhibitor for ulcer therapy, according to the present invention, provides rapid and effective therapy, surpassing that of conventional treatments. In addition, doses can be reduced, in comparison with administration of either drug alone.

CLAIMS

1. A medicine which comprises a combination of a protein possessing cell growth factor activity with a proton pump inhibitor.

2. A medicine of claim 1, wherein the protein possessing cell growth factor activity is a protein possessing fibroblast growth factor activity.

3. A medicine of claim 2, wherein the protein possessing fibroblast growth factor activity is a protein possessing basic fibroblast growth factor activity.

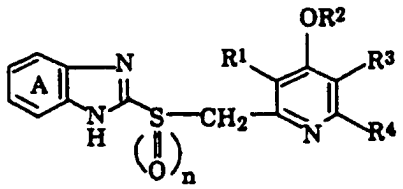
4. A medicine of claim 3, wherein the protein possessing basic fibroblast growth factor activity is acid-resistant.

5. A medicine of claim 3, wherein the protein possessing basic fibroblast growth factor activity is a basic fibroblast growth factor (bFGF) mutein showing enhanced acid stability as a result of replacement of at least one bFGF-constituent cysteine with another amino acid.

6. A medicine of claim 5, the bFGF mutein is the recombinant human bFGF mutein CS23 in which cysteine residues at the 70- and 88- positions are replaced by serine residues.

7. A medicine of claim 1, wherein the proton pump inhibitor is a benzimidazole compound.

8. A medicine of claim 7, wherein the benzimidazole compound is a compound of the formula:



wherein ring A may optionally be substituted, R^1, R^3 and R^4 are, the same or different, hydrogen, or an alkyl or alkoxy

group, R^2 is a hydrocarbon group which may optionally be substituted, and n is 0 or 1, or a salt thereof.

9. A medicine of claim 8, wherein the compound is lansoprazole.

10. A medicine of claim 1, which comprises a combination of the mutein CS23 with lansoprazole.

11. A medicine of claim 1, which is used to prevent or treat an ulcer.

12. A medicine of claim 11, wherein the ulcer is a peptic ulcer.

13. A medicine of claim 1, which is a kit which comprises a protein possessing cell growth factor activity and a proton pump inhibitor.

14. A medicine of claim 1, which is a pharmaceutical composition which comprises a protein possessing cell growth factor activity and a proton pump inhibitor.

15. A method of producing a pharmaceutical composition which comprises admixing a protein possessing cell growth factor activity with a proton pump inhibitor.

16. Use of a combination of a protein possessing cell growth factor activity with a proton pump inhibitor for the manufacture of a medicine for the prevention or treatment of an ulcerating disease.

17. A method for preventing or treating a ulcerating disease of a mammal, which comprises administering an effective amount of a protein possessing cell growth factor activity in combination with an effective amount of a proton pump inhibitor to the mammal.

18. A method of use of a proton pump inhibitor for enhancing a protein possessing cell growth factor activity.